Chiral α-substituted α-hydroxy acids

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CHAPTER III

A NEW ^{1}H NMR METHOD FOR DETERMINATION OF THE ENANTIOMERIC EXCESS OF α-SUBSTITUTED α-HYDROXY ACIDS

3.1 *INTRODUCTION*

Not only in synthetic organic chemistry, but also in many branches of biochemistry and pharmacology there is a growing interest in optically active compounds. Reliable methods for determination of enantiomeric excesses (e.e. 's) of the chiral compounds are important for all these areas. Chiefly during the last three decades a large number of powerful analytical methods have been developed for ascertaining the enantiomeric excess. Before that time, polarimetry[1] was the method most frequently employed. Polarimetry gives the optical rotation of chemical substances, which is a bulk property rather than a method that provides independent information about both enantiomers, including their ratios. Polarimetry gives therefore, optical purities[a] rather than enantiomeric excesses. Moreover, there are some additional serious shortcomings to this technique. Knowledge of the absolute rotation of the compound with unknown optical purity is a prerequisite. Furthermore, the optical rotation can be very sensitive to parameters, such as temperature, concentration and solvent.[2] And finally, the relationship between optical purity and enantiomeric excess is not always linear.[3] Nowadays, mainly thanks to NMR spectroscopy, much more reliable stereochemical analyses can be performed. In fact, methods have become available in which from one analytical experiment not only the enantiomeric excess but also the absolute configuration of a chiral compound can be determined.[4] In these methods, NMR is used to distinguish between diastereomeric compounds or complexes in solution using the fact that diastereomeric nuclei have different NMR chemical shifts. This magnetic nonequivalence has been induced by chiral solvents,[5] chiral shift reagents,[6] and

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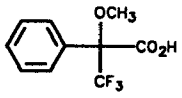
[a] optical purity describes the ratio of the optical rotation of the mixture of enantiomers to that of the pure enantiomer.

derivatizing reagents (chiral and achiral) used to prepare diastereomeric compounds.[7,8,9,10] In this chapter we describe a chiral derivatizing reagent which can be employed in the determination of the enantiomeric excess of α-substituted α-hydroxy acids (or their esters). Although chiral chromatographic techniques[11] are steadily more useful for e.e. determination, a discussion of these methods falls beyond the scope of this chapter.

3.2 *ESTABLISHING THE ENANTIOMERIC EXCESS BY FORMATION OF DIASTEREOMERIC COMPOUNDS*

After the introduction of NMR spectroscopy it became apparent that the property of diastereomeric compounds to give NMR signals with different chemical shifts can be advantageously employed in determining the ratio of these compounds. This ratio may easily be measured by integration of the signals resulting from the diastereotopic groups. In order to determine the composition in enantiomeric mixtures, the enantiotopic groups have to be converted to diastereotopic groups. As already mentioned in the previous Section this can be accomplished by the use of an appropriate chiral derivatizing reagent which converts enantiomers to a pair of diastereomers. Raban and Mislow[12] were the first who reported such a reagent. The enantiomeric excess of chiral acids (as their acid chlorides) was established by the use of optically pure o-fluorophenylethanol. The presence of the fluoro atom also enables, in addition to ^{1}H NMR, the use of ^{19}F NMR for analysis.

A very versatile chiral derivatizing reagent was proposed by Dale, Dull and Mosher:[13] α-methoxy-α-trifluoro-methylphenylacetic acid (MTPA, **301**). This reagent, commonly known as Mosher reagent, is still successfully being used (mostly as the acid chloride) for the determination of the enantiomeric excess of alcohols and amines.



301

The following conditions must be satisfied for a chiral derivatizing reagent to

furnish a reliable measurement of the diastereomeric ratio: (a) The reagent must be chemically and optically stable under the conditions of the derivatization process. (b) No kinetic resolution should occur during the derivatization reaction. (c) In the isolation procedure no enrichment of the diastereomeric mixture should take place. (d) The chemical shifts of the diastereotopic groups, selected for analysis, should differ sufficiently to allow accurate integration.

Since the discovery of Mosher reagent, several other new chiral derivatizing reagents, which meet the criteria outlined above, have been developed. Some of them are depicted in Figure 3.1.[14,15,16,17,18]

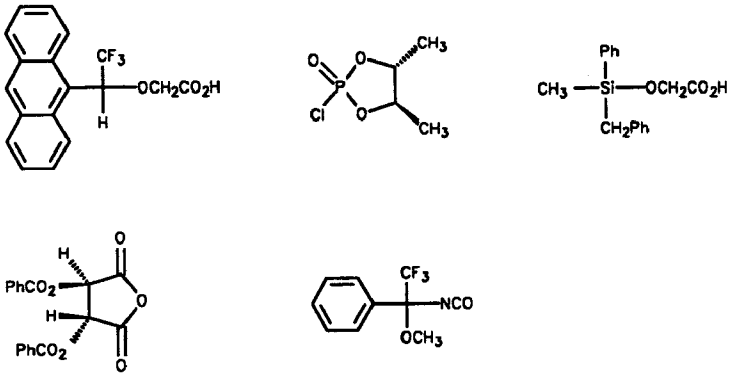
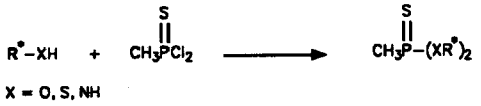


Figure 3.1

A method for the enantiomeric excess determination of chiral alcohols, thiols and amines that does not require an optically pure auxiliary reagent, has been reported by Feringa et al. a few years ago.[8,9] Combining the principle of Horeau[19] with ^{31}P NMR led to the achiral derivatizing agents such as PCl_3, $CH_3P(=O)Cl_2$ and $CH_3P(=S)Cl_2$. In this method a chiral racemic substrate is converted to diastereomeric phosphonates. Owing to the presence of the stereogenic phosphorus atom, two different meso compounds and one d,l pair are formed (Scheme 3.1).

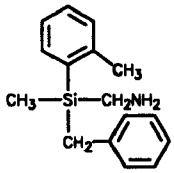


Scheme 3.1

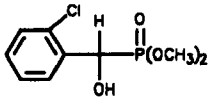
Although a wide variety of alcohols, thiols, amines and carboxylic esters have been successfully coupled and analyzed using the reagents mentioned above, these methods have mostly been limited to coupling of primary and secondary compounds. Only a few examples of the e.e. determination of tertiary or highly hindered compounds using derivatizing reagents are known.[20,21] During our study of new chiral α-substituted α-hydroxy acids (and esters), which can be regarded as tertiary hydroxy derivatives, we required a method to determine the enantiomeric purity of these compounds. However, as to be expected from the literature, coupling of these sterically hindered compounds with several derivatizing reagents, including MTPA chloride, PCl_3 and $CH_3P(=O)Cl_2$ failed.

3.3 *CHIRAL DERIVATIZING REAGENTS FOR THE DETERMINATION OF THE ENANTIOMERIC EXCESS OF CHIRAL CARBOXYLIC ACIDS*

Only a few reports have appeared on the determination of the enantiomeric excess of chiral acids using a derivatizing reagent. Terunama and coworkers[16] reported the use of optically active benzylmethyl-o-tolylsilylmethylamine (**302**) as a suitable reagent for chiral carboxylic acids. Smaardijk[22] proposed optically pure phosphonate **303** as derivatizing reagent. However, no acids with the carboxylic group attached to a tertiary carbon atom have been derivatized with these compounds. Furthermore, elaborate derivatization procedures involving refluxing conditions, which place severe demands on the optically and chemically stability of the derivatizing reagents, have been employed.



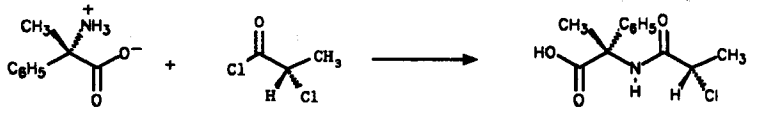
302



303

A very suitable chiral derivatizing reagent for establishing the enantiomeric composition of α-alkylated α-amino acids was discovered by Kellogg et al.[7] (S)-2-chloropropanoyl chloride (**304**) was coupled with a secondary or tertiary amino acid,

using a simple and fast derivatization procedure to give a N-acylated diastereomeric product which was analyzed by ^1H NMR spectroscopy. An example of this methodology is depicted in Scheme 3.2.



304

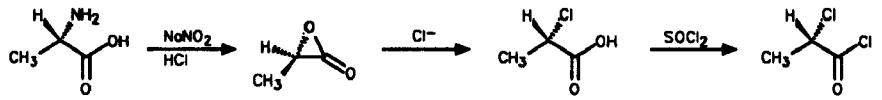
Scheme 3.2

On the basis of this work, we applied this reagent, which seems suitable for coupling with sterically hindered compounds, for ascertaining the enantiomeric excess of α-alkylated α-hydroxy acids.[23]

3.4 *(S)-2-CHLOROPROPANOYL CHLORIDE AS CHIRAL DERIVATIZING REAGENT*

3.4.1 *Synthesis and coupling of the reagent*

(S)-2-Chloropropanoyl chloride (**304**) was conveniently synthesized following literature procedures.[24] Thus, diazotation of L-alanine (**305**) in 6N HCl afforded (S)-2-chloropropanoic acid (**306**) in 70% chemical yield. This conversion is known to proceed with overall retention of configuration, due to two inversion steps.[25] The initially formed diazonium salt is believed to undergo an intramolecular substitution reaction (with inversion of configuration) to give α-lactone **307**, which is subsequently ring-opened in an intermolecular S_N 2 process (again with inversion of configuration) to afford (S)-**306** which was isolated in 75% chemical yield. (Scheme 3.3)

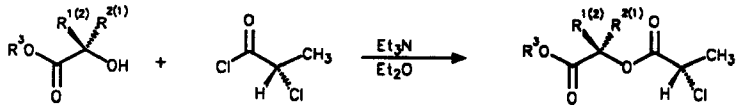


(S)-305 (R)-307 (S)-306 (S)-304

Scheme 3.3

The desired derivatizing reagent (S)-**304** was obtained from (S)-**306** after treatment with thionyl chloride. The compound can be stored at -10 °C for at least four weeks without showing measurable racemization.

Several α-substituted α-hydroxy acids (or esters) were acylated with (S)-**304** according to the reaction depicted in Scheme 3.4. Unlike the derivatizing procedure employed for α-amino acids, which involves coupling under more elaborate Schotten-Bauman conditions[7], the α-hydroxy compounds react quickly and quantitatively (based on ^{1}H NMR) in diethyl ether as solvent and in the presence of triethylamine to afford O-acylated products **308**. The ^{1}H NMR spectrum of these diastereomeric products were recorded and analyzed.



304 308

Scheme 3.4

3.4.2 *Enantiomeric excess determination of the acylated α-hydroxy compounds*

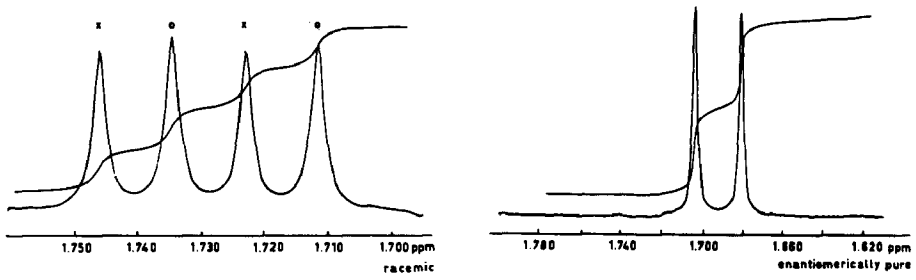
Table 3.1 summarizes the relevant ^{1}H NMR data for (S)-2-chloropropanoyl derivatives (**308**) of a variety of racemic α-hydroxy acids and esters. The chiral derivatizing reagent contains in principle the methyl group as a useful probe for the enantiomeric excess determination. The ^{1}H NMR spectra of the derivatized non-enantiomerically pure α-hydroxy compounds revealed in general two doublets for the $\underline{CH_3}CHCl$ absorptions, with coupling constants varying from 6.7-7.2 Hz. The chemical shift differences of the two doublets generally ranged from 0.01 to 0.07 which makes these differences easily distinguishable with 300 MHz NMR. Integration of the signals of the diastereomeric groups provides an indirect measure of the original enantiomeric composition of the α-hydroxy compound.

Table 3.1: ^{1}H NMR *data for (S)-2-chloropropanoyl derivatives* ***308.***

entry	R^1	R^2	R^3	$\Delta\delta^a$	J(Hz)	solvent
1	C_6H_5	$CH_2CH{=}CH_2$	H	0.01	7.0	$CDCl_3$
				0.01	7.2	CD_3OD
2	C_6H_5	$CH_2CH{=}CH_2$	Et	0.01	7.2	CD_3OD
				no separation		$CDCl_3$
3	C_6H_5	$CH_2C(CH_3){=}CH_2$	H	0.03	6.9	CD_3OD
				no separation		$CDCl_3$
				0.01	6.9	C_6D_6
4	C_6H_5	$CH_2CH{=}CHC_6H_5$	H	0.01	6.9	$CDCl_3$
				0.07	7.2	C_6D_6
5	C_6H_5	$CH_2C_6H_5$	H	0.03	7.0	C_6D_6
6	C_6H_5	CH_3	H	0.01	6.9	$CDCl_3$
				0.07	7.2	C_6D_6
				0.01		C_6D_6[b]
7	C_6H_5	$-(CH_2)_4-$	Me	0.01	6.8	CD_3OD
				0.06	6.7	C_6D_6
8	CH_3	CH_2CH_3	H	0.03	7.0	$CDCl_3$
				0.01	6.8	C_6D_6
				no separation		CD_3OD
				0.04		C_6D_6[b]
9	CH_3	$CH_2CH{=}CH_2$	H	0.02	6.8	C_6D_6
				no separation		CD_3OD
				0.03		CD_3OD[b]
10	CH_3	$CH_2CH(CH_3)_2$	Me	no separation		C_6D_6
				0.02	6.8	C_6D_6[c]
11	CH_3	$CH_2CH{=}CHCH_3$	H	0.02	6.9	C_6D_6

a: Difference in chemical shift of the $\underline{CH_3}CHCl$ (or other indicated) absorptions.
b: The ^{1}H NMR spectrum revealed two well separated signals for the methyl group of the α-hydroxyacid; the chemical shift differences for these methyl signals are given.
c: Only the $CH_3\underline{CH}Cl$ absorption could be assigned unambiguously; the chemical shift differences for these are given.

Figure 3.2 shows as an example the $\underline{CH_3}CHCl$ absorptions in the ^1H NMR spectra of racemic and enantiomerically pure α-allyl mandelic acid derivatized with (S)-2-chloropropanoyl chloride (**304**).



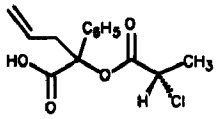


Figure 3.2

To test the accuracy of this method mixtures, varying in molar compositions, of available enantiomerically pure α-hydroxy compounds were prepared. The enantiomeric ratios of these mixtures were independently determined by ^1H NMR and compared with optical purity measurements. In all these cases agreement within 2% could be achieved. These experiments exclude possible racemization of the derivatizing reagent under the coupling conditions. Furthermore, ratios for racemic compounds were 50:50 with 2% error which establishes that no kinetic resolution occurs during acylation.

The solvent in the experiments can be critical for obtaining well resolved signals. However, in most of the cases it was possible to achieve sufficient signal separation by selecting the proper solvent. Due to anisotropy effects a greater signal separation may be observed especially when aromatic solvents are used.[26] If, howe-

ver, a sufficient signal separation of the $\underline{CH_3}CHCl$ absorptions is not obtained the two quartets resulting from the $CH_3\underline{CH}Cl$ absorptions were used for determining the diastereomeric ratio (entry 10). This probe is especially suitable if interference of the $\underline{CH_3}CHCl$ absorption with signals from the α-hydroxy compound itself occurs.

Finally, we observe that in some cases an isolated CH_3 group, present in the α-hydroxy compound, gives two well separated singlets after derivatization. Integration of these signals provides an additional means for determination of the diastereomeric ratio (entries 6, 8 and 9). The results demonstrate that (S)-2-chloropropanoyl chloride (**304**) is a useful chiral derivatizing reagent according to the criteria mentioned in Section 3.2.

3.4 *CONCLUDING REMARKS*

The method presented here enables the determination of the enantiomeric composition of sterically hindered α-hydroxy acids and esters. (S)-2-chloropropanoyl chloride is a convenient reagent for obtaining diastereomeric derivatives of these α-hydroxy compounds, the diastereomeric ratio of which can be established by ^1H NMR. This ratio reflects the original enantiomeric composition of the α-hydroxy compound.

3.5 *EXPERIMENTAL SECTION*

General Remarks: All ^1H NMR spectra were recorded on a Varian VXR-300 spectrometer (at 300 MHz).

General procedure for derivatizing a chiral α-hydroxy acid (or ester) with (S)-2-chloropropanoyl chloride (304). To a stirred solution of the α-hydroxy acid (or ester) (0.5 mmol) and triethylamine (0.6 mmol) in 1 mL of diethyl ether was added at 0 °C (S)-**304** (0.6 mmol). After stirring for 15-30 minutes, the mixture was filtered to remove the triethylamine hydrochloride and concentrated under vacuum. The O-acylated product was then taken up in the solvent of choice for NMR determination of the diastereomeric ratio.

3.6 *REFERENCES*

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